# Selection and optimisation of biventricular pacing: the role of echocardiography

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The quantification of ventricular dyssynchrony is a key factor in identifying patients with severe heart failure who may benefit from cardiac resynchronisation with biventricular pacing (BVP). Echocardiographic techniques appear to offer superior sensitivity and specificity than the ECG in selecting these patients. This paper reviews the scope of current echocardiographic techniques for guiding both patient selection and optimisation of device programming following implantation.

Biventricular pacing (BVP) or cardiac resynchronisation therapy (CRT) is an adjuvant treatment for patients with symptomatic, drug refractory heart failure, providing both acute and long term haemodynamic and functional improvements.[1–4]

The 12 lead ECG has formed the mainstay of patient selection for BVP. A broad QRS complex provides a marker for electrical delay that may correlate with the mechanical dyssynchrony that BVP can correct. However, this selection strategy results in a failure of 20–30% of implanted patients to respond clinically[5] and excludes a number of patients with a narrow QRS complex who may benefit from BVP. In addition, devices are costly and implants time consuming and not without risk, an 8% serious adverse event rate having been recently reported.[4] Therefore, non-invasive screening techniques that offer superior sensitivity and specificity for diagnosing ventricular dyssynchrony or incoordination are essential for patient selection. It is likely that the answers to many of these key issues in BVP lie in the expanding role of echocardiographic techniques. This paper aims to review the use of echocardiography in guiding patient selection and in the process of therapy optimisation.

## LEFT BUNDLE BRANCH BLOCK AND VENTRICULAR DYSSYNCHRONY

Twenty to 30% of patients with symptomatic congestive heart failure have ECG evidence of conduction delay in the form of left bundle branch block (LBBB).

LBBB reflects an abnormal sequence of activation, with systole and diastole of the left ventricle being notably delayed, compared with right ventricular (RV) activation. The mechanical consequences of this abnormal pattern of depolarisation have greatest adverse effect on the interventricular septum, resulting in paradoxical septal movement,[6] (fig 1) and significant reductions in regional septal and global ejection fraction[7] (fig 2). Unlike dyskinesis, where there is no delay in systolic wall excursion, ventricular dyssynchrony is characterised by regions of early and late left ventricular (LV) contraction. Most commonly, the interventricular septum contracts early relative to the delayed contraction of the posterolateral free wall. Failure of simultaneous contraction of opposing LV walls reduces peak systolic pressure (LV ±dP/dt) in early systole and early diastole. As a result, both aortic and mitral valve opening may be delayed and the proportion of the cardiac cycle occupied by LV ejection and filling is significantly decreased. The temporal constraints in LV filling result in further reduction in stroke volume and cardiac output (fig 3A).[8] Dyssynchronous ventricular contraction is further complicated by the presence of regional wall motion abnormalities in patients with underlying myocardial ischaemia.

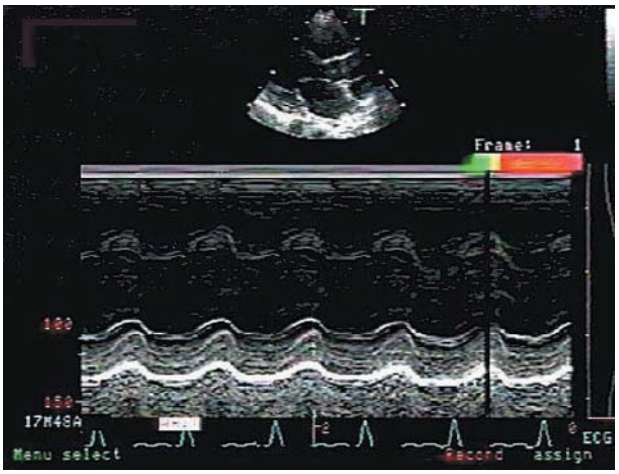


**Figure 1** M mode echocardiogram showing paradoxical left ventricular septal wall contraction and late systolic/early diastolic thickening of the posterior wall.

In patients with dilated cardiomyopathy (DCM), dyssynchrony has also been shown to induce or prolong ''functional'' mitral regurgitation.[9] For effective mitral valve closure, a sufficient transmitral pressure gradient is required combined with effective ventricular contraction. The presence of ventricular dyssynchrony and poor systolic function reduces the peak systolic pressure (LV dP/dt) and hence transmitral pressure gradient, causing insufficient mitral valve closing forces and functional mitral regurgitation.[10] A prolonged PR interval, commonly found in these patients, delays ventricular contraction and further reduces the effective mitral valve closure thereby exacerbating mitral regurgitation.[11] In these patients, diastolic mitral regurgitation with pre-systolic or post-systolic components is often observed (fig 4).

Significant interventricular conduction delay is assumed with a broad LBBB on the ECG, but one in five patients with

**Abbreviations:** BVP, biventricular pacing; CRT, cardiac resynchronisation therapy; IVPI, interventricular pacing interval; LBBB, left bundle branch block; LV, left ventricular; RV, right ventricular; TDI, tissue Doppler imaging; VTI, velocity time integral

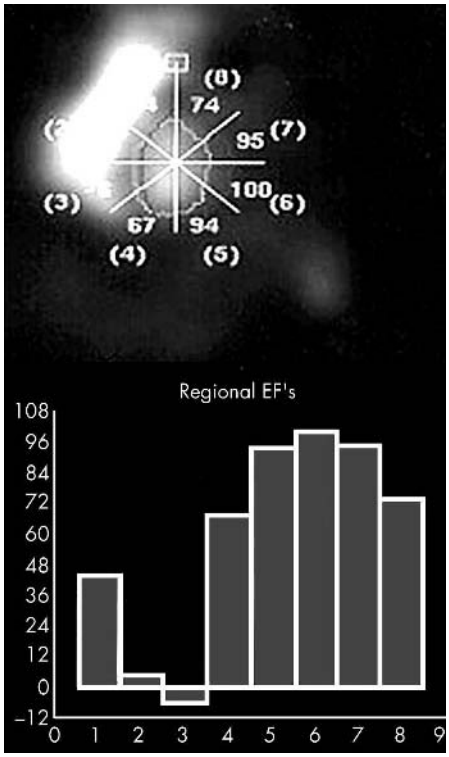


**Figure 2** Reduction in regional ejection fraction (septal regions 2 and 3) on MUGA scan in the patient in fig 1.

LV ejection fraction $\leqslant$ 35% and QRS duration $\geqslant$ 150 ms have no evidence of LV dysyynchrony.[12] Similarly, recent data have suggested that a significant proportion (around 50%) of patients with heart failure and "normal" QRS duration ($<$ 120 ms) have intraventricular dyssynchrony,[13] and may improve following BVP.[14] It has been shown that systolic improvement and mechanical resynchronisation do not require electrical synchrony[15] and correcting mechanical rather than electrical dyssynchrony is of prime importance. Echocardiography guided techniques, which enable quantitative and non-invasive assessment of ventricular mechanical dyssynchrony, offer a potential solution to this problem.

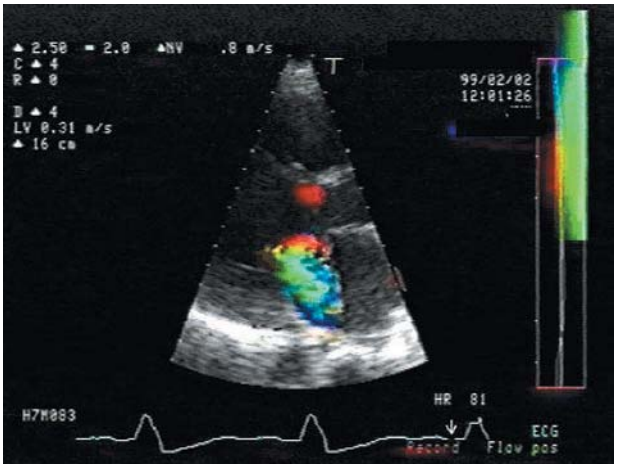


**Figure 4** Presystolic mitral regurgitation in the patient from fig 1. The arrow indicates the frame is acquired before onset of the QRS complex.

There are numerous ways of assessing ventricular dyssynchrony using echocardiography; the more commonly used parameters are described below.

### Atrioventricular dyssynchrony

This may be assessed by measuring the ventricular filling time from the onset of the E wave to the end of the A wave on transmitral pulsed wave Doppler (fig 3A). An LV filling time of $<$ 40% cardiac cycle or R-R interval is indicative of atrioventricular dyssynchrony. This may occur as a consequence of ventricular dyssynchrony or due to a prolonged PR interval.[16]

### Inter- and intraventricular dyssynchrony

Incoordination of different segments of the left ventricle or intraventricular dyssynchrony should be distinguished from interventricular dyssynchrony, which implies a delay between RV and LV contraction. Many of the benefits observed following BVP are related to improved synchrony of contraction within the left ventricle. It is therefore important when selecting patients for BVP to determine the degree of dyssynchrony within the left ventricle (intraventricular dyssynchrony). Preliminary findings suggest it may

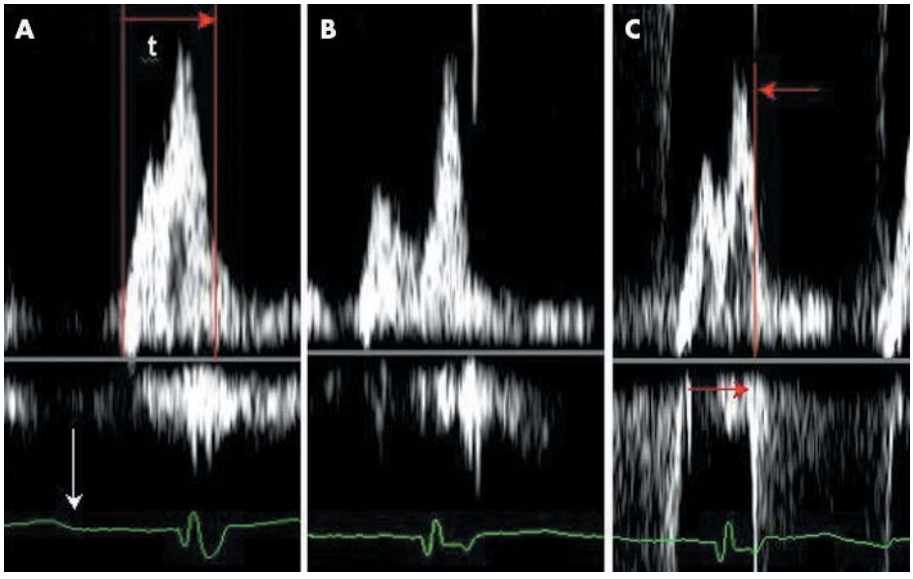


**Figure 3** Optimisation of atrioventricular delay. Left ventricular (LV) inflow pulsed wave Doppler at the level of mitral valve leaflets. (A) Atrioventricular (AV) delay 160 ms: uniphasic transmitral flow (fused E and A wave) with reduced left ventricular filling time (t) $<$ 40% R-R interval. The onset of filling is delayed commencing after the end of the T wave on the ECG (white arrow). (B) AV delay 90 ms: mitral valve closure line coincides with the end of the A wave maximising LV filling time and restoring biphasic transmitral flow with E and A wave separation. (C) AV delay 70 ms: the end of the A wave is now truncated by mitral valve closure (seen arrowed and aliasing), with the commencement of mitral regurgitation and reduced LV filling time. AV optimisation can now be improved by increasing the AV delay in 10 ms increments until mitral valve closure line coincides with the end of the A wave without truncation.

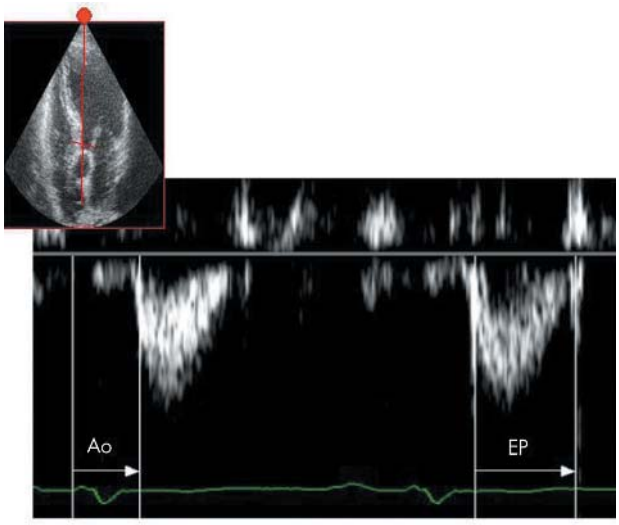


**Figure 5** Aortic pre-ejection time (Ao) is measured as the time from QRS onset to blood flow. The time from the aortic valve opening to closure represents the ejection period (EP).

be possible to identify regional contractile delay using multiplane two dimensional or three dimensional echocardiography at frame rates as low as 25 Hz. To date, however, tissue Doppler imaging (TDI) has been used most extensively to study ventricular dyssynchrony.

## Prolonged aortic pre-ejection time

A prolonged aortic pre-ejection time (> 140 ms) measured as the time from QRS onset on the ECG to start of Doppler flow in the aortic outflow tract is considered a marker of intraventricular dyssynchrony[16] (fig 5). The ejection period, measured as the interval between aortic valve opening and closure, may also be reduced due to the increased duration of isovolumic relaxation and contraction.

## Prolonged interventricular mechanical delay

Using pulsed wave Doppler, pulmonary pre-ejection delay can be measured as the time from QRS onset to the start of pulmonary blood flow. The difference between aortic and pulmonary pre-ejection times provides a measure of interventricular mechanical delay and is considered abnormal with values greater than 40 ms.[16]

## Tissue Doppler imaging

TDI is a modification of conventional colour Doppler technology in which directional velocity signals arising from the tissues are analysed. Tissue Doppler velocities may be displayed either in colour encoded two dimensional mode, M mode, or as a spectral pulse (fig 6).

Both inter- and intraventricular dyssynchrony can be measured using pulsed wave TDI. Traces can be acquired from the septum, lateral, anterior, inferior, anteroseptal and posterior LV walls using an apical four, two, and three chamber view. During the cardiac cycle, the cardiac apex remains relatively fixed[17] and from an apical window, motion of the base of the heart is in the axial plane. This is nearly parallel with the Doppler cursor, with velocities obtained almost entirely representing motion due to longitudinal contraction and relaxation.[18] Deflections above the baseline reflect motion towards the transducer, while those below the baseline reflect motion away from the transducer. Regional electromechanical delays can be measured from QRS onset to either the start or peak systolic shortening (S wave) (fig 6). Some studies have simply used the delay between septal and

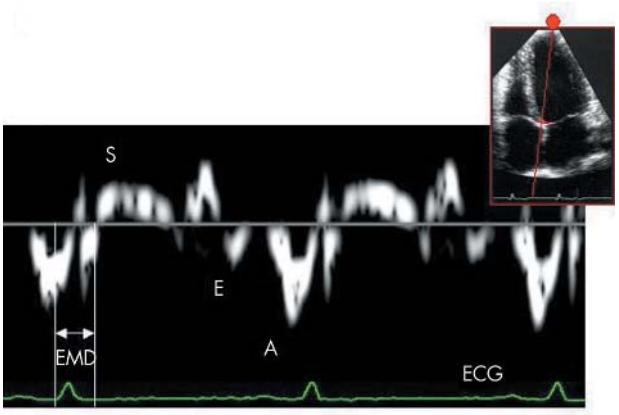


**Figure 6** Pulsed wave tissue Doppler imaging of the basal interventricular septum acquired from an apical four chamber view. A broad complex QRS is seen. The upward deflection following QRS complex represents longitudinal shortening toward the transducer during ventricular systole (S wave). The two main deflections below the baseline represent E and A waves occurring during ventricular filling as the sampled region moves away from the transducer at the cardiac apex. The heights of S, E, and A waves (cm/s) measure the velocities of motion of the sampled region during systole and diastole respectively. Regional electromechanical delay (EMD) may be calculated from the start of QRS to the onset or peak of the S wave.

either the posterior or lateral wall as a guide to intraventricular dyssynchrony,[19 20] but this assumes the septum to be the earliest site of contraction and the posterior or lateral wall the latest. A more accurate assessment of the dispersion of intraventricular contraction can be calculated by analysing differences between all the different LV regions.

The dispersion of intraventricular contraction can be calculated as the time between latest and earliest sites of LV contraction, providing a measure of intraventricular dyssynchrony. It has been shown that in normal control patients, regional systolic contraction is highly synchronised, occurring within 40–50 ms.[21] Dispersion of > 40–50 ms may therefore provide an index of intraventricular dyssynchrony, but is by no means definitive evidence of dyssynchrony.

Interventricular dyssynchrony can be quantified using similar methodology, by including pulsed wave TDI recorded from the RV free wall at the level of the tricuspid valve annulus and calculating the maximal dispersion between RV and LV contraction.

## M mode echocardiography

Using either M mode echocardiography or TDI, delays in segmental longitudinal contraction can be demonstrated by measuring the time from QRS onset to the end of systolic contraction. A delay in regional wall contraction exists if contraction continues after closure of the aortic valve (measured with pulsed Doppler in the aortic outflow tract)—that is, after the onset of diastole. Similarly, regional wall contraction is delayed if contraction ends after the onset of ventricular filling (measured by time from QRS onset to the start of the E wave on transmitral Doppler) with consequent coexistence of systole and diastole.[16]

Alternatively, a parasternal short axis M mode at the level of the papillary muscles may be used to calculate the septal-to-posterior wall motion delay (measured as the time from the maximal posterior displacement of the anterior septum to the maximum contraction of the posterior wall). A delay of > 130 ms of this parameter was shown to predict reverse remodelling after BVP with a positive predictive value of 80%, and may offer an alternative means for guiding patient selection.[20]

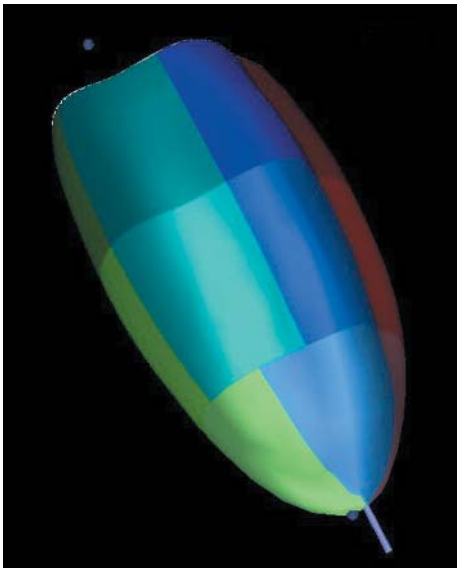

**Figure 7** Three dimensional reconstruction of the left ventricle, which is divided into different regions. The timing of contraction and relaxation is assessed for each of these regions.

### Tissue tracking, strain rate analysis, and three dimensional echocardiography

Colour TDI and three dimensional reconstruction have been used to demonstrate improved myocardial synchrony, cardiac performance, reductions in LV volumes, reduced mitral regurgitation, and increased forward stroke volume following BVP.[22 23] (figs 7, 8, and 9)

Using colour TDI, digitally recorded loops of one or more cardiac cycles can be used to provide velocity data from the entire myocardium. This has led to the development of the TDI derived modalities of tissue tracking and strain rate analysis. Tissue tracking visualises the longitudinal motion amplitude in each myocardial segment during systole in a colour coded format and has been used to determine the extent of myocardium with delayed longitudinal contraction.

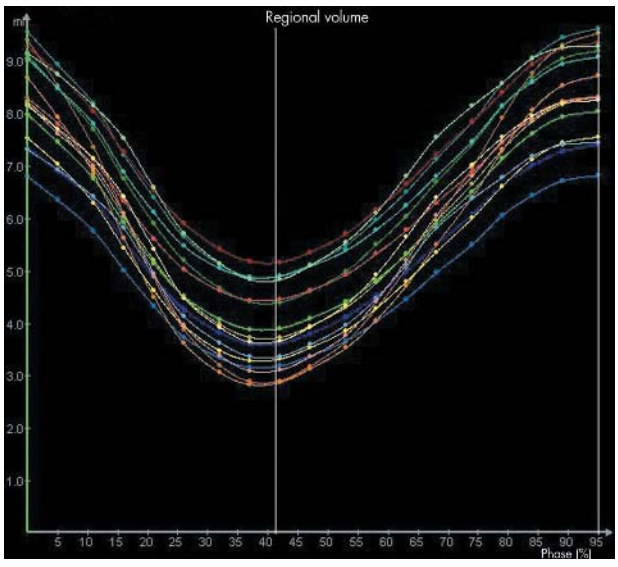


**Figure 8** Echocardiographic assessment of left ventricular dyssynchrony. Each line represents movement of one of the left ventricular segments shown in fig 7. This ventricle contracts synchronously.

It has been demonstrated that the greater the number of segments displaying delayed longitudinal contraction or contraction during diastole (after closure of the aortic valve) the more severe the degree of dyssynchrony, and was found to be predictive of short term efficacy of BVP.[23]

One limitation of TDI is that it does not distinguish between active and passive wall motion. Strain rate analysis helps in differentiating this and therefore provides more accurate information on regional myocardial contractile function. This technique can be used in addition to tissue tracking before BVP to confirm true shortening in regions showing delayed longitudinal contraction. Following BVP, the number of segments showing delayed longitudinal contraction was significantly reduced, while recruitment of this contractile reserve translated to improved systolic function.[24]

Advances in three dimensional echocardiography have enabled accurate measurements of LV volumes and quantification of volumetric flow. Using this technique, BVP has been shown to reduce LV end diastolic and end systolic volumes and mitral regurgitation. LV forward stroke volume is increased following BVP and this is attributed to improved LV synchrony of contraction and reduced mitral regurgitation. The percentage increase in LV forward stroke volume was found to independently predict percentage improvement in walking distance following BVP.[22]

## EFFECTS OF BIVENTRICULAR PACING

The aim of BVP in heart failure is to reduce mechanical dyssynchrony, thereby enabling the heart to contract more efficiently, increase LV ejection fraction and cardiac output, but with less work and lower oxygen consumption.[25] Various mechanisms that account for the haemodynamic improvements seen with BVP have been suggested.[26]

Improvements which correlate with echocardiographic changes may be observed following BVP including: increased LV filling time with separation of E and A waves on transmitral Doppler; a reduction in severity of mitral regurgitation in particular the presystolic component; increased ejection fraction; increased aortic velocity time integral; increased myocardial performance index; reduced septal dyskinesia; and reduced ventricular dyssynchrony as measured by TDI[10 27 28] (fig 6). Reverse remodelling has been

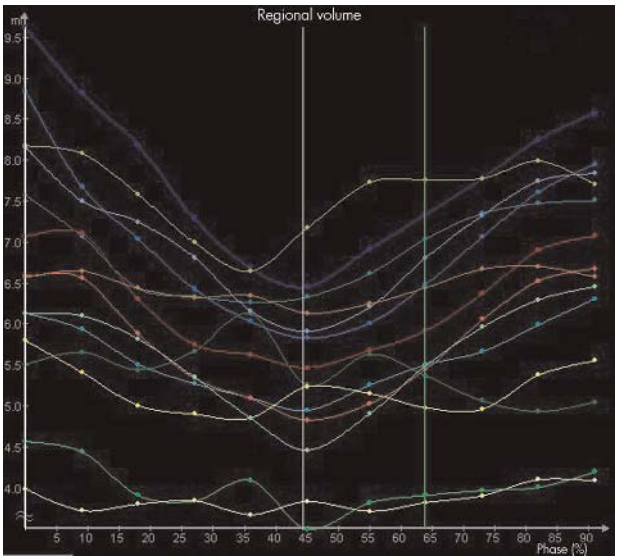


**Figure 9** Echocardiographic assessment of left ventricular dyssynchrony. This shows an abnormal, dyssynchronous ventricle.

observed in patients chronically following BVP, with reductions in LV end diastolic and end systolic diameters and volumes being associated with improvements in cardiac function.[29]

## Echocardiographic techniques used in optimising biventricular pacing

### Patient selection

The first prospective study of the selection of candidates based on mechanical as opposed to electrical criteria reported clinical improvement in 85% of patients.[16] The inclusion criteria for device implantation were measurements of dyssynchrony calculated from standard pulsed Doppler and M mode techniques. In a more recent study, the presence of combined intra- and interventricular dyssynchrony, as measured by pulsed wave tissue Doppler imaging, were shown to be the best predictive factors of LV functional recovery and reversed remodelling after BVP. A value of 102 ms for the sum of inter- and intraventricular dyssynchrony was found to provide the optimal predictive accuracy with sensitivity, specificity, and accuracy of 96%, 77%, and 88%, respectively. This parameter was also found to correlate closely with improvements in LV ejection fraction, and end diastolic and end systolic diameters after resynchronisation, while QRS duration had no significant association with any parameter.[30]

### Guiding LV lead placement

Preliminary evidence suggests that optimal improvements in LV performance may be achieved when pacing at the most delayed site.[31] TDI enables identification of the site of delayed LV contraction and may be useful in guiding LV lead placement at implantation. However, in practical terms, the site of LV pacing is often limited by individual coronary venous anatomy.

### Atrioventricular optimisation

Several acute pacing studies have demonstrated the importance of a short atrioventricular (AV) delay in providing haemodynamic benefit, most notably in patients with first degree heart block and presystolic mitral regurgitation.[11 32–34] However, the detrimental haemodynamic effects of RV pacing due to ventricular dyssynchrony are now well recognised. In such patients with heart failure and conventional indications for pacing, BVP may be considered as a preferred treatment.[35] The optimisation of AV delay following pacemaker implantation has traditionally been achieved using Doppler echocardiography.[36] If not dependent on atrial pacing, optimisation should be performed at the patient's intrinsic heart rate. Starting with a long AV delay, such that there is intrinsic conduction and no biventricular pacing, transmitral pulsed wave Doppler is measured. The AV delay is then gradually reduced in 20 ms intervals and the LV filling time (t) measured (fig 3A). This is done until the end of the A wave on transmitral flow coincides with the closure of the mitral valve. There should be a progressive lengthening of LV filling time with separation of the E and A waves. The mitral regurgitation time is reduced with eradication of the presystolic component (fig 3B). Too short an AV delay, seen by the truncation of the A wave by mitral valve closure, is also suboptimal and will again reduce the LV filling time (fig 3C).

Alternatively, the AV delay can be programmed, guided by the aortic velocity time integral (VTI) with the maximum VTI recorded being defined as the optimal AV delay.[37]

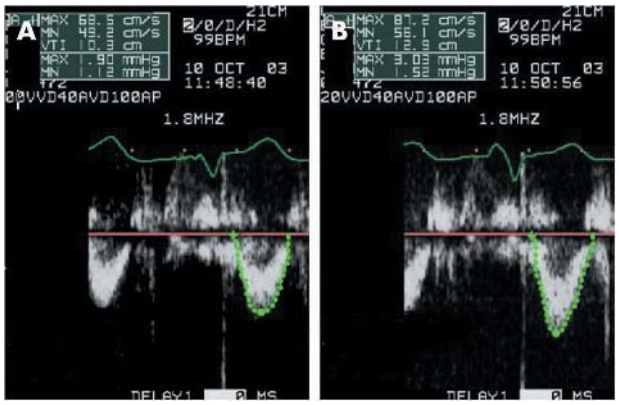


**Figure 10** (A) LV velocity time integral (VTI) of 10.3 cm with an optimised AV delay at an interventricular pacing interval (IVPI) of 0 ms. (B) The same patient with an LV VTI of 12.9 cm at an IVPI delay of 20 ms (LV ahead of RV).

### Interventricular pacing interval optimisation

In more advanced biventricular pacemakers it is now possible to alter the interventricular pacing interval (IVPI), to allow either LV or RV preactivation. Evidence now suggests that in many patients, optimal haemodynamic benefits are observed with sequential BVP and appropriate programming of the IVPI guided by echocardiographic techniques post-implantation.[38 39] The IVPI can be adjusted to provide the maximal forward stroke volume as measured by the aortic VTI (fig 10); however, more research is required in this area.

## Local practice

With the expansion in echocardiographic modalities and specialised computer software, the options for guiding patient selection before BVP and optimisation after device implantation continue to grow. In addition, the numbers of patients being referred for device therapy for heart failure are expected to rise, and while there are no definitive recommendations for assessing patients, it is important for centres to develop a comprehensive local practice using available techniques and expertise. Pulsed wave tissue Doppler imaging is one of the most promising echo techniques for guiding patient selection and is relatively easy to use; it is one of the key assessments in the protocol used in our institutions.[40] We suggest a protocol for the echocardiographic selection of patients for BVP (see Appendix). The ''St Mary's protocol'' was developed following a literature review of current evidence based data in conjunction with local research data and expertise, which is currently being formally evaluated. Fulfilling the protocol criteria provides a high probability of dyssynchrony and identifies patients likely to benefit from BVP. By applying this protocol to patients implanted in our institution, retrospective analysis found that 88% had benefited symptomatically with a reduction in New York Heart Association (NYHA) functional class.

In patients with heart failure who do not have dyssynchrony but require pacing for other reasons, we would suggest that implantation of a biventricular system is strongly considered since pacing via a right ventricular lead is likely to induce dyssynchrony.

## CONCLUSION

BVP may provide significant symptomatic benefit for selected patients with severe symptomatic heart failure. Until recently patients have only been considered for device therapy on the grounds of 12 lead ECG QRS duration. With the expansion and advancement of echocardiographic techniques, more sensitive and specific tools for quantifying ventricular dyssynchrony now exist. In the future it is likely that these parameters will be increasingly used to guide patient selection and optimise haemodynamic benefits following

pacemaker implantation. Reverse remodelling in ventricular function can be assessed by echocardiography and may prove useful in monitoring patient response and long term clinical outcome.

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## APPENDIX: ST MARY'S PROTOCOL FOR GUIDING PATIENT SELECTION FOR BIVENTRICULAR PACING

### ESSENTIAL CRITERIA

- Symptomatic heart failure (NYHA III–IV)
- Optimal medical treatment
- Poor LV systolic function: ejection fraction < 35% (Simpson's rule on 2D echo)
- Exclusion of reversible causes of systolic heart failure
- Optimal revascularisation
- Selection for BVP requires the presence of:
  - two major criteria
  - one major and three minor
  - four minor

### MAJOR CRITERIA

- Tissue Doppler imaging evidence of intraventricular dyssynchrony.
  - increased intraventricular dispersion of mechanical contraction >55 ms
- Tissue Doppler imaging evidence of combined intra- and interventricular dyssynchrony
  - sum of intraventricular and interventricular dispersion of mechanical contraction >100 ms

### MINOR CRITERIA

- Tissue Doppler imaging evidence of intraventricular dyssynchrony (if not used as a major criterion)
  - increased intraventricular dispersion of mechanical contraction > 40 ms
- Tissue Doppler imaging evidence of interventricular dyssynchrony (if not used as part of a major criterion)
  - increased interventricular dispersion of mechanical contraction > 40 ms
- Reduced LV filling time < 40% cardiac cycle
- Prolonged aortic pre-ejection time > 140 ms
- Traditional Doppler evidence of interventricular mechanical delay > 40 ms
- QRS duration > 130 ms

This protocol has not been formally validated but takes into account much of the available evidence. It is recommended as a guide for selecting patients only. Meeting the guidelines provides a high probability of dyssynchrony and a likely benefit from BVP. Using this protocol 88% of patients implanted in our institution have symptomatically benefited.

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